

REMARKS

I. Applicant's Claim Amendments.

Applicant has cancelled, without prejudice, certain claims directed to a non-elected invention. Applicant expressly reserves the right to pursue the subject matter of the cancelled claims through the filing of one or more divisional applications.

Applicant has added new dependent claims 21-24. Support for these new claims is set forth in the specification, as filed (See, e.g. page 1 of the Specification). Prompt entry of these new claims is respectfully requested.

II. Examiner's 35 U.S.C. 112, second paragraph rejection.

Claims 2-4, 6 and 17-20 are present in this case. Applicant has added new claims 21-24 herein. Reconsideration is respectfully requested. Applicant proffers the following remarks in response to Examiner's rejection of claims 19 and 20 based on 35 U.S.C. 112, second paragraph, that use of the term "substantially" rendered the claims indefinite.

The invention lies in the finding that prodrugs comprising a carrier moiety selected from cinnamoyl, benzoyl, phenylactyl, 3,4-methylenedioxycinnamoyl and 3,4,5-trimethoxycinnamoyl, chemically linked to a therapeutic polypeptide, aa_n, wherein aa is an amino acid and n is an integer from 2 to 10, through a non-therapeutic linker species, i.e., an amino acid, wherein the therapeutic polypeptide is one that is not *substantially* absorbed following oral administration, can be orally administered to provide effective therapeutic levels.

Examiner asserts that "substantially" is a relative term, not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant responds by pointing out that the Federal Circuit has held that the word "substantial" is not indefinite when used in conjunction with a term used to describe a particular characteristic. MPEP § 2173.05(b)(D). For example, in *Andrew Corporation v. Gabriel Electronics, Inc.*, the Federal Circuit explained that a patentee is not required to "establish the exact point at which a change in the physical phenomenon occurs." 847 F.2d 819, 822-23 (Fed. Cir. 1988). In *Andrew* the court held that use of the phrase "substantially equal" in a claim to an antenna did not render the claim indefinite because one of ordinary skill in the art would

understand the metes and bounds of the claim. *Id.* Additionally, in *Verve, LLC v. Crane Cams, Inc.*, the Federal Circuit held that expressions such as “substantially” are warranted in order to accommodate the minor variation that may be appropriate to secure the invention.” 311 F.3d 1116, 1120 (Fed. Cir. 2002).

In light of the above holdings, Applicant respectfully submits that one of ordinary skill in the art would understand that in light of the specification, the phrase “substantially not absorbed” as used in the claim indicates a peptide therapeutic that when administered orally is not absorbed in amounts sufficient to result in a biologically therapeutic effect. In other words, in the absence of the carrier moiety, bioavailable amounts of the peptide are too low to be therapeutically effective. As previously mentioned, the current invention is directed to providing a means of modifying a peptide therapeutic so that it may be administered orally, and absorbed in amounts sufficient to be therapeutically effective.

In addition, the language of the specification supports this construction. The “Background” section indicates that poor absorption of a peptide directly relates to its poor bioavailability. That section provides an example of a peptide that is “poorly” absorbed, and also defines “moderate oral bioavailability” as less than 25 %. Therefore, one of ordinary skill in the art would understand that “substantially not absorbed following its oral administration” refers to a peptide drug with a bioavailability of below 25 %, and the invention is directed towards use in these circumstances. Therefore, the claims, read in light of the specification, reasonably apprise those skilled in the art as to the metes and bounds of the claimed invention, and are as precise as the subject matter permits. The court in *Hybritech Inc. v. Monoclonal Antibodies* held that, where one of ordinary skill would understand the scope of the claims, as a matter of law no court can demand more. 802 F.2d 1367, 1385 (Fed. Cir. 1986).

In light of the above comments, Applicant respectfully requests that the Examiner reconsider the claims at issue, and withdraw the 112, second paragraph, rejection.

III. Examiner’s 35 U.S.C. 103(a) Rejection.

Examiner also rejects claims 2-4, 6, and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Goldstein (US 4,396,606) in view of Bundgaard et al. (US 4,694,006) (“Bundgaard”). In addition to Applicant’s previous arguments against this ground for rejection,

Applicant respectfully proffers the following additional comments in support of Applicant's view that Examiner's 103 rejection should be withdrawn. Reconsideration is respectfully requested.

A. The Goldstein Patent.

Goldstein is directed to improving the in vivo half-life, and efficacy of polypeptide analgesics having opioid activity, and particularly enkephalins. Goldstein teaches that improving the opioid activity can be accomplished through the addition of novel oligopeptides containing alternating basic hydrophilic amino acids and hydrophobic amino acids (having at least five units), to the carboxyl terminus of the polypeptide opioid. In particular the Examiner states that the "reference teaches met-enkephalin, and teaches that there has been substantial activity in trying to develop modifications of the compound to enhance the *activity*."

Additionally, as acknowledged by the Examiner, Goldstein fails to teach the advantageous utility of a carrier moiety, a critical element of the instant invention, and/or the combination of an amino terminal-linked carrier and non-therapeutic linker.

B. The Bundgaard Patent.

Bundgaard teaches use of an acyl-containing carrier moiety for improving the aqueous solubility of the *drug*, allopurinol, for oral administration. In addition, the Bundgaard patent provides a list of chemical moieties that may be linked to allopurinol by way of the acyl group to form a prodrug with increased solubility for oral, anal, or parenteral delivery.

The Bundgaard patent does not teach or suggest the use of a carrier for increased bioavailability of a peptide therapeutic, and/or the use of a non-therapeutic linker.

C. Applicant's Comments Regarding Examiner's 103(a) Rejection.

To overcome the insufficiency of either the Goldstein or Bundgaard patents to teach every element of the current invention, the Examiner has, based on her interpretation of the references, concluded that it would have been obvious to have modified the opioid of Goldstein by linking with acyl groups such as cinnamoyl or benzoyl because of the expectation of successfully producing a "prodrug" of met-enkephalin for improved solubility and oral administration.

Applicant respectfully submits that the Examiner has not carried the burden of establishing a *prima facie* case of obviousness to support a 103 rejection. MPEP § 2142. The Examiner has the initial burden of factually supporting any conclusion of obviousness. The three essential criteria that must be established to substantiate an obviousness rejection are: (1) there *must* be some suggestion or motivation in the reference themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings; (2) there *must* be a reasonable expectation of success; and (3) the reference must teach or suggest *all* the claim limitations. It is an impermissible use of hindsight to combine pieces of the prior art to argue that a claimed invention is obvious. There must be something in the prior art that suggested the combination of these particular prior art devices and processes other than the hindsight gained from knowing that the inventor chose to combine these particular things in this particular way. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir. 1988).

(1) There is no suggestion or motivation in the prior art references or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings in the manner proposed by the Examiner.

Goldstein and Bundaard address vastly different pharmacological obstacles and lack any suggestion to combine their teachings to address the very different, and longstanding problem of peptide therapeutic absorption in the mammalian gut that is the critical concept addressed by the current invention. Specifically, Goldstein addresses the problems of peptide-therapeutic *in vivo* half-life, and efficacy through the addition of a carboxy terminus oligopeptide containing alternating basic and hydrophobic residues. However, the Goldstein patent does not mention or purport to address the well-known problem of poor gastro-intestinal absorption of peptide therapeutics. In fact, Goldstein presumes that the peptide therapeutic is already present in the bloodstream.

The Examiner points out that the Goldstein invention includes a “phenolic hydroxyl linked to polypeptide with at least one amino acid.” However, the Examiner ignores the fact that this phenolic group is present as a side chain component of the tyrosine residue that is an intrinsic part of the enkephalin peptide. Any other reference in Goldstein to the use of a phenolic group is in the context of alternative opioids that could be used with the carboxy-terminal

peptide to enhance analgesic activity. ('606 Patent, Col. 4, lines 28-34). Nothing in Goldstein would suggest to one of ordinary skill in the art that the phenol side chain of tyrosine, or the addition of another phenol-containing compound, could serve as a carrier and increase absorption of a peptide drug in the gastrointestinal tract. In fact, Goldstein teaches that the phenolic group is likely to mediate opioid receptor binding, in essence, teaching away from the current invention. ('606 Patent, Col. 1, lines 42-45; and Col. 2, lines 11-23).

Bundgaard addresses the issues of oral, parenteral, and rectal bioavailability related to a specific small molecule drug through the use of an acyl-containing carrier molecule. There is nothing in the Bundgaard patent that teaches or suggests that phenolic moiety, much less cinnamoyl or benzoyl, would be useful in increasing oral bioavailability of a peptide drug. The mere presence of the element of the invention in prior art references without more (i.e. the suggestion or motivation to combine and the reasonable likelihood of success) is not sufficient to maintain a prima facie case of obviousness. The mere fact that references can be combined or modified does not render the combination obvious unless prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). Furthermore, the level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999).

The Examiner makes no claim that the cited prior art references contain any suggestion to combine or modify their teachings. However, Applicant contends that there is also nothing in the cited prior art that would even motivate one of ordinary skill in the art *at the time of the invention* to combine or modify the teachings. As discussed above, Goldstein is directed only to increasing the analgesic activity (i.e. efficacy) of a peptide drug once it is introduced to the site of action. To address this specific problem, Goldstein teaches use of a polypeptide chain that consists of an amino-terminal tyrosine residue, a therapeutic peptide, and a carboxy-terminal peptide of alternating basic hydrophobic and hydrophilic residues. There is nothing in Goldstein that would motivate one of ordinary skill at the time of the present invention to use cinnamoyl or benzoyl linked through a non-therapeutic amino terminal linker in order to address the seemingly impossible challenge of increasing oral absorption of peptide drugs. To suggest this motivation existed, the Examiner relies on the teachings of Bundgaard which address the unrelated problem of attempting to increase the lipid/water solubility of a specific small molecule drug that, alone,

is 70 % absorbed by oral dose. Thus, the Bundgaard patent lacks not only the suggestion that use of the carrier moieties would affect bioavailability of other small molecule drugs, but it doesn't even purport to address poorly absorbed small molecule drugs. As such, it is only through the use of hindsight that one could support a contention that Bundgaard's disclosure could provide the motivation to use cinnamoyl or benzoyl to address the entirely different problem of increasing the bioavailability of poorly absorbed peptide drugs.

The Examiner also asserts that "acyl groups such as benzoyl and cinnamoyl are *well known* carrier molecules." However, when an examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory **must** be provided. *In re Grose*, 592 F.2d 1161, 1168 (CCPA 1979). Here, the Examiner provides no evidence for this assertion other than indicating the location in the Bundgaard "laundry list" where the terms "benzoyl," and "cinnamoyl" appear. In an instance similar to the current case, the court in *Fujikawa v. Wattansin* held that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. 93 F.3d 1559, 1571 (Fed. Cir. 1996). Thus, in the current situation the Examiner's conclusion that one of ordinary skill in the art would be motivated to select the benzoyl and cinnamoyl moieties to solve the problem of peptide drug absorption cannot be maintained.

(2) Based on the uncertainty of the chemical and biological sciences, and the knowledge of one of ordinary skill at the time of the invention, a conclusion that the prior art provided a reasonable expectation of success at the time of the invention cannot be factually supported.

"Whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Providing evidence of a reasonable expectation of success is difficult where, as here, the claimed invention involves the application of an unpredictable technology. *Genetech, Inc. v. Novo Nordisk*, 108 F.3d 1361 (Fed. Cir. 1997). Under patent law, obviousness and expectation of success are evaluated from the perspective of a

person having ordinary skill in the art at the time of the invention. While later publications may explain what was known earlier, it would be wrong to impute later- recognized insights--or possible obstacles--to the knowledge available to those skilled in the art at the time of the invention. *Velander v. Garner*, 348 F.3d 1359 (Fed. Cir. 2003). As the court opined in *Velander*, “the case boils down to the question of whether, as of the critical date, one of ordinary skill in the art would have had a reasonable expectation of success...” What that means is that there must be “(i) substantial evidence that (ii) supports the [Board's] conclusion that it was more probable than not that, as of the critical date, one of ordinary skill in the art would have had a reasonable expectation of success...” *Id.* at 50. The Examiner in this case conspicuously fails to provide any support whatsoever for the assertion that a reasonable expectation of success existed. The Examiner provides no indication how the combination of Goldstein and Bundgaard would reasonably lead a person of ordinary skill at the time of the invention to expect that the problem of peptide drug absorption in the mammalian gut, which has effectively precluded oral delivery of peptide drugs heretofore and on into the present day, could have been successful.

In addition, it is a well-established axiom of patent law that the applicant is entitled to be his own lexicographer, and where not expressly defined, the terms in a patent are to be given their plain and ordinary meaning which would be understood by one of ordinary skill in the art “in light of the specification of which they are a part.” *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1575 (Fed. Cir. 1986); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 (Fed. Cir. 1996). Where the terms used in a patent are understood from the specification, it is improper for the PTO to: (i) interpret claim terms so broadly that such interpretation conflicts with the meaning given to identical terms in other patents from analogous art or (ii) to use extrinsic evidence in construing the term.

The Bundgaard patent expressly defines the term “prodrug” as “a derivative of allopurinol...” US Patent 4,694,006, Col. 1, lines 13-15. However, it would be understood by a person of ordinary skill in the art that the Applicant in the present case uses the term “prodrug” to encompass a carrier moiety, a linker, and a peptide therapeutic. The Examiner states that “the function of the cinnamoyl and benzoyl carrier to enhance bioavailability of a *drug* is taught in the Bundgaard reference.” (emphasis added). The Examiner’s statement mischaracterizes the current invention by suggesting that a peptide therapeutic is the functional equivalent of a small molecule drug. If the term “prodrug” is properly construed as it is used in the current

Application, there is simply no teaching or suggestion in the prior art nor an expectation of success in combining the cited references.

The Office Action contains several contradictory statements that further demonstrate that the current 103 rejection is improper, and untenable. The Examiner first states “that the drug used in Bundgaard is not the same or similar to the polypeptide of Goldstein,” and then states that “the function of the cinnamoyl and benzoyl carrier to enhance bioavailability of a *drug* is taught in the Bundgaard reference.” In addition, the Examiner later expressly admits that the current invention deals with a “polypeptide drug....” Thus, by the Examiner’s own admission, a DRUG, as it is used in the Bundgaard patent is different from the peptide therapeutic of the current application (and the Goldstein patent). It is therefore erroneous for the Examiner to attempt to ignore this admitted distinction by stating that Bundgaard teaches the acyl-containing “cinnamoyl and benzoyl carriers as moieties for *prodrugs*...” in order to establish a basis for inferring that an expectation of success exists. Through this error, the Examiner draws a parallel that is not only contrary to the understanding of one of ordinary skill in the art, but which also goes against conventional distinctions made by those in the technical field.

In this case, the Examiner is using “impermissible hindsight” to draw a parallel between the effects of a carrier molecule on a *drug*, per se, such as allopurinol, and the effects of a cinnamoyl or benzoyl moiety (which was not specifically tried or claimed by Bundgaard) on a polypeptide therapeutic. To lump both a hydrophobic small molecule (i.e., allopurinol) and a polypeptide together under the generic usage of the word “drug” for the purpose of asserting that a reasonable expectation of success existed is to ignore the essential, and critical, chemical and physical distinctions between these two types of therapeutics.

For example, the convention in pharmaceutical research is to distinguish “small molecule *drugs*” from “antibody” and “protein therapeutics” precisely because of the disparate challenges associated with each respective form in the development and method of delivery to patients. Moreover, problems of oral administration of peptide therapeutics are so empirically borne out that biotech and pharmaceutical companies do not even pursue oral delivery methods unless those routes include the primary target tissue. (See for example, Controlled release and local delivery of therapeutic antibodies. *Expert Opin Biol Ther.* 2004 Jul;4(7):1029-44)

One need not be of ordinary skill in the art to recognize the fact that currently available oral therapeutics consist nearly entirely of small molecule drugs. This is because of the widely recognized and vastly different problems associated with peptide therapeutic viability and absorption in the gut of mammals. Therefore, one skilled in the art would surely appreciate that, because of the uncertainties involved in pharmaceutical research (in particular *in vivo* research), and the chemical and physically distinct mechanisms involved in drug absorption and polypeptide therapeutic absorption, the simple fact that a carrier moiety increases the bioavailability of a small molecule drug is, *a priori*, essentially meaningless with respect to a polypeptide.

In addition to the improper use of hindsight, the outstanding section 103 rejection amounts to no more than an “obvious to try” rejection. The Court of Appeals for the Federal Circuit has held that “obvious to try” is not the proper test to apply in using the criterion of obviousness of Patent Code § 103. The obstacles that typically preclude oral administration of peptide therapeutics continue to this day, and this fact further supports the notion that success could not have been reasonably expected. Hence, even if it is arguable that the references might have provided one skilled in the art the motivation to try, it is a monumental leap of faith to argue that a “reasonable expectation of success” also existed in this case. The fact that the current invention also claims the use of the amino terminal linker, a feature neither taught nor contained in either of the cited references, highlights the significance of the overall invention, and further evidences the uncertainty and unpredictability of the art.

(3) The cited references do not teach or suggest each and every element of the claimed invention. *In re Royka*, 490 F.2d 981 (CCPA 1974).


Neither the Goldstein reference nor the Bundgaard reference discusses the use of an amino terminal peptide linking the carrier molecule to the therapeutic peptide. In fact, one of ordinary skill in the art would likely conclude that, as a competent scientist, Goldstein must have tried an amino terminal linker and observed no significant or positive effects in his experiments, which also suggests he failed to appreciate its significance in solving the problem addressed by the current invention. Furthermore, neither of the references teaches anything relevant to the absorption of a peptide therapeutic. In fact, as mentioned earlier, the Goldstein patent is

specifically concerned with optimizing the activity of an injectable peptide therapeutic. 4,396,606 Patent, Col 1, lines 26-36.

In conclusion, the current invention is directed to solving a problem neither taught nor suggested by either reference, which is increasing the absorption of a peptide drug by oral administration. Even if one were to combine the teachings of the two cited prior art references, the combination would not result in the currently claimed structure which includes the three elements of a cinnamoyl or benzoyl moiety linked through a non-therapeutic linker species to a therapeutic polypeptide. Therefore, the Examiner has failed to establish that the cited references teach every element of the current invention.

In view of the presented arguments and added dependent claims, it is respectfully submitted that the application is now in condition for allowance and notification to this effect is respectfully requested.

Respectfully submitted,

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DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

DOCKETED	<u>11/12/04</u>
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STATUTORY DATE	<u>1/1/05</u>

Office Action Summary



Application No.

09/844,426

Applicant(s)

ZIMMER, ROBERT H.

Examiner

Gina C. Yu

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on December 10, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-4, 6 and 8-20 is/are pending in the application.
- 4a) Of the above claim(s) 8-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4, 6, 17-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

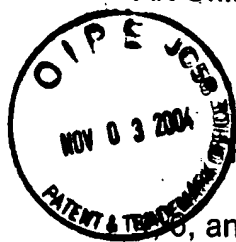
Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Receipt is acknowledged of Amendment filed December 10, 2003. Claims 2-10, and 8-20 are pending, of which claims 8-16 have been withdrawn from consideration. Obvious double patenting rejection as indicated in the previous Office action dated September 9, 2003, is withdrawn in view of terminal disclaimer filed December 10, 2003. Claim rejections made under 35 U.S.C. § 112, second paragraph, as indicated in the same Office action, are withdrawn in view of claim amendment, and new rejection is made. Claim rejection made under 35 U.S.C. § 102(e) as indicated in the same Office action is withdrawn in view of applicants' remarks. Claim rejection made under 35 U.S.C. § 103 (a) are withdrawn to address the claim amendment, but the substance of the claim rejection is maintained for the reasons of the record and as explained below.

Terminal Disclaimer

The terminal disclaimer filed on December 10, 2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of copending application no. 10/237,254 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 6, and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The term "substantially" in claims 19 and 20 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The remaining claims are rejected as depending on indefinite base claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 2-4, 6, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Goldstein (US4396606) in view of Bundgaard et al. (US 4694006) ("Bundgaard").

Goldstein teaches opioid compounds having a phenolic hydroxyl linked to polypeptide with at least one amino acid. The reference teaches met-enkephalin and teaches that there has been substantial activity in trying to develop modifications of the compound to enhance the activity. See col. 1, lines 13 – 17.

The Goldstein reference fails to teach the carrier moiety of the instant claims.

Bundgaard teaches methods for preparing the prodrug form of allopurinol and thereby to provide improved aqueous solubility and oral administration compared to the parent compound. See col. 1, line 6 – col. 2, line 47. The reference teaches that

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acyl groups such as benzoyl and cinnamoyl are well known carrier moieties. See col. 5, line 66 – col. 7, line 54; col. 10, line 60- col. 11, line 18.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the opioid of Goldstein by linking with acyl groups such as cinnamoyl or benzoyl because of the expectation of successfully producing a prodrug of met-enkephalin for improved solubility and oral administration.

Response to Arguments

Applicant's arguments filed December 10, 2003 have been fully considered but they are not persuasive in part.

Applicants argue that the combination of Goldstein and Bundgaard fails to teach the claimed prodrug. Specifically, applicants assert that the cinnamoyl and benzoyl carrier moieties in Bundgaard are not the most preferred compounds in the reference. It is well known in patent law a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 U.S.P.Q. 2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). It is also held that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. The court in *In re Susi* also held that "a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." See 440 F.2d 442, 169 U.S.P.Q. 423 (C.C.P.A. 1971). In this case, using cinnamoyl and benzoyl carrier moieties to make a prodrug cannot be a patentable simply because the prior art prefers other moieties. It is true that the drug used in Bundgaard is not

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the same or similar to the polypeptide of Goldstein. However, the function of the cinnamoyl and benzoyl carrier to enhance bioavailability of a drug is taught in the Bundgaard reference.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, the fact that the polypeptide drug and cinnamoyl and benzoyl carriers as moieties for prodrugs are found in the cited references only. The rejection is solely based on the teachings of the references and not improper hindsight reasoning.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory

Art Unit: 1617

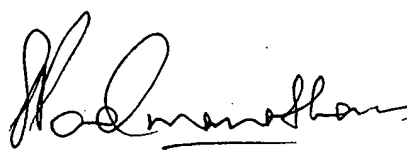
action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gina C. Yu whose telephone number is 571-272-0635. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gina Yu
Patent Examiner


6/25/09


SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER